REMARKS

Reconsideration of the present application is respectfully requested. Claims 2-10, 12, 14, and 16-34 are pending after the amendment. Claims 15 and 35 have been cancelled. Applicants reserve the right to pursue the content of these claims in a continuing application. Claims 9, 12, 14, and 25 have been amended. Support for the amendments is found in the claims as originally filed, and throughout the specification. No new matter has been added.

Rejections under 35 U.S.C. §112, 1st Paragraph, Enablement:

Claims 2-8, 12, 14-16, 18-26, and 28-35 are rejected under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, the Examiner asserts that the specification, while being enabling for nucleic acids of SEQ ID NO: 1 or that encode SEQ ID NO: 2, does not reasonably provide enablement for nucleic acids that have 90% identity to SEQ ID NO: 1, that encode a protein that has 90% identity to SEQ ID NO: 2, that hybridize to SEQ ID NO: 1, that encode any 25 amino acids of SEQ ID NO: 2, or that comprise any 50 contiguous nucleotides of SEQ ID NO: 1. This rejection is maintained for the reasons of record, and Applicants arguments were not persuasive.

The Examiner asserts that the instant specification only provides guidance for construction of a cDNA library from B73 maize line (example 1), sequencing random clones from the cDNA library (example 2), BLAST analysis of the sequences (example 3) to identify those with homology to *Arabidopsis* RAD51C (example 4). It is also asserted that the instant specification fails to provide guidance for exact hybridization or amplification conditions and probes/primers to use in isolation of nucleic acids, and further fails to provide guidance for which amino acids of SEQ ID NO: 2 can be altered to maintain RAD51 activity of the encoded protein. The Examiner cites Lazar *et al.* (1998, MCB 8:1247-1252) and Hill *et al.* 1998, BBRC

244:573-577) as teaching that the effects of amino acid substitutions are not predictable, and that the mutated proteins would have at least 95% identity to the original protein, and the nucleic acids would hybridize under high stringency conditions.

Applicants respectfully disagree. The specification does reasonably provide enablement for nucleic acids of claim 12 having 90% sequence identity to SEQ ID NO: 1, and the nucleic acids of claim 25 that encode a protein having 90% sequence identity to SEQ ID NO: 2, and nucleic acids of claim 14 that selectively hybridize under explicit high stringency conditions to the full length complement of SEQ ID NO: 1. Applicants disclosure of SEQ ID NOS: 1-6 fully supports claim 15, directed to nucleic acids comprising at least 50 contiguous nucleotides of SEQ ID NO: 1, and claim 35, directed to nucleic acids which encode at least 25 contiguous amino acids of SEQ ID NO: 2. However, in order to expedite prosecution, claims 15 and 35 have been cancelled in the current amendment. In the current amendment, claims 12, 14, and 25 have been amended to recite that the encoded polypeptide is "involved in DNA double strand break repair". Support for this amendment is found on pages 1-4, which describe the function of Rad51C, and the Rad51 family, specifically support is found on page 2, line 22 – page 3, line 2, and page 4, lines 7-11.

Contrary to the Examiner's assertions, guidance in the specification for these claims is not limited to Examples 1-4 as pointed to by the Examiner, guidance is found throughout the specification as well as in the Examples and in the art, as pointed our in Applicants response filed 4/8/02. Applicants have disclosed SEQ ID NOS: 1-6, which represent three independent nucleic acid sequences and their encoded proteins. For example, besides Examples 1 and 2, Applicants provide extensive guidance on nucleic acid library construction, isolation and evaluation in the specification (see, for example, page 6, lines 1-11; page 11, lines 23-32; page 14, line 30 – page 15, line 3; page 26, lines 9-27; and pages 33-37). The guidance on sequence analyses, comparison, identity and identification of homologues is not limited to Examples 3 and 4, (see, for example, page 9, lines 4-8; page 17, line 28 –

page 22, line 15; page 28, line 27 – page 29, line 4; and page 60, lines 10-26). The specification also provides guidance on codon degeneracy, silent variants, and preferences (page 7, lines 15-28; page 8, line 22 – page 9, line 3; and page 58, lines 4-29), guidance on conservative variants and amino acid substitutions (page 7, line 12 – page 8, line 17; and page 24, lines 21-30), and well as discussion of known homologues, interactions, functions and conserved regions (pages 1-4). Assays for function for Rad51 family members were known in the art at the time of filing, as shown on page 14 in the response filed 4/8/02, the screens include complementation of mutations, screens for interactions such as yeast two-hybrid screens, and co-immunoprecipitation, induction of expression in response to DNA damage, and enhancement of recombinase activity.

Besides the guidance listed above and pointed to in previous responses, Applicants have also submitted Appendices C and D (see response filed 4/8/02) which provide papers disclosing the 3-D structure of a protein in the Rad51 family, and a multiple sequence alignment of the protein sequences of the present invention with several members in the Rad51 family. Applicants submit another multiple sequence alignment herein (Appendix E) which shows a global alignment of the proteins of the present invention with other Rad51C proteins known at the time of filing, as well as a partial RadA/Rad51C protein. One of skill in the art would prepare and use these alignments, much like what was done by Lazar and Hill as discussed below, to identify conserved, partially conserved, and non-conserved amino acid residues, and to predict whether a conservative or non-conservative amino acid substitution would likely significantly impact the function of the modified protein compared to an unmodified protein. Also, one of skill in the art could also use the three-dimensional model of the related protein to identify amino acids residues and potential acceptable substitutions.

Lazar discloses modifications to a human transforming growth factor α (TGFα) sequence, Hill discloses modifications to a ADP-glucose pyrophosphorylase sequence. Applicants wish to point out that both references use the known

homology to related proteins to identify and target particular amino acid residues. The references used homology to predict important conserved amino acids where substitution with another amino acid would likely have an impact on the activity of the protein. For example, Lazar study shows that even conservative substitution of L48 with similar amino acids (M or I) dramatically impacted activity, as predicted by the observed absolute conservation of leucine (L) at this position. In all cases, the modified protein had to be screened for the effect(s) of the modification. Clearly, one of skill in the art does believe that structural identity, as well as the presence of functional domains and conserved motifs are predictive of polypeptide function, as is clearly demonstrated by the pervasive use of sequence searching algorithms such as BLAST, FASTA, and the like, and multiple sequence alignment programs such as CLUSTAL and PileUp, and the like. In the instant application, as claimed, the structural identity, *i.e.* percent sequence identity is not the only criteria used, the disclosure also points out conserved functional motifs known in the art and the claims further recite a functional limitation that the encoded polypeptide is involved in DNA double-strand break repair. If the sequences of Lazar or Hill were similarly claimed, while the modified sequences may hybridize to the original sequence, they would not meet the functional limitation for activity, and therefore would be explicitly excluded by the claim.

The Examiner asserts that undue experimentation is required by one of skill in the art and that one of skill in the art would be required to make and test all possible single amino acid substitutions, which for the 294 amino acid long protein encoded by SEQ ID NO: 1 would require making and analyzing greater than 19^{294} nucleic acids. The Examiner further asserts that undue trial and error experimentation would be required to screen through the plants transformed with the myriad of nucleic acids encompassed by the claims.

Applicants respectfully disagree that undue experimentation is required to practice the instant invention. Applicants have defined the sequences by their physical or chemical properties as taught by Amgen Inc. v. Chugai Pharmaceutical

Co. Ltd. 18 USPQ 2d 1016 at 1021 (Fed. Cir. 1991). The claimed nucleic acid sequences are defined by their structure, *i.e.* percent sequence identity to SEQ ID NO: 1 or percent sequence identity of the encoded polypeptide to SEQ ID NO: 2, and further defined by their functional activity, *i.e.* polypeptides involved in DNA double strand break repair. One of skill in the art would not be required to generate every single random nucleotide or amino acid substitution in order to make and use the invention. Using the knowledge in the art of other known sequences and assays, and Applicants disclosure of SEQ ID NOS: 1-6, and guidance provided in the specification regarding other known sequences, conserved motifs, codon degeneracy, codon preferences, conservatively modified variants, conservative amino acid substitutions, nucleic acid library construction, nucleic acid amplification, hybridization, sequence analyses and comparisons, vector construction, and plant transformation, one of skill in the art can readily practice the full-breadth of the claimed invention.

The question of experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is the amount of experimentation must not be unduly extensive. *PPG Inc. v. Guardian Industries Corp.* (37 USPQ 1218, 1623, (Fed. Cir. 1996). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (1982 PTOBA).

With the guidance provided in the present specification, one skilled in the art can readily practice the full-breadth of the claimed invention. Therefore, it is respectfully requested that the rejection of claims 2-8, 12, 14-16, 18-26, and 28-35 under 35 U.S.C. §112, first paragraph be withdrawn.

Rejections under 35 U.S.C. §112, 1st Paragraph, Written Description:

Claims 2-10, 12, 14-16, 18-26 and 28-35 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not sufficiently described in the specification to indicate the inventor(s) had possession of the invention.

The Examiner asserts that the Applicant has not described the structural features, *i.e.* the sequence of a nucleic acid having 90% identity to SEQ ID NO: 1 or that encodes a polypeptide having 90% sequence identity to SEQ ID NO: 2. The Examiner further asserts the specification does not describe the 50 contiguous nucleotides or 25 contiguous amino acids encompassed by the claims, and does not describe nucleic acids that hybridize to SEQ ID NO: 1 under the claimed conditions. The Examiner asserts that the claims do not follow the format of Example 14, because 90% identity is not the 95% identity used in Example 14, and "participates in a complex which enhances recombinase activity" is not a specific description of function as used in the Guidelines.

Applicants respectfully disagree as this rejection was applied to the claims, and how this rejection may be applied to the claims as amended. In order to expedite prosecution, claims 12, 14, and 25 have been amended to recite functional language wherein the polynucleotide encodes a polypeptide involved in DNA double strand break repair. Before and after amendment, the claims do follow the format of Example 14 in the Guidelines. The claims recite a defined structural parameter, *i.e.* percent sequence identity, and further recite a functional requirement, *i.e.* encoding a polypeptide involved in DNA double strand break repair. This functional requirement is the specific description of the function of Rad51C, which is believed to be one of the components of the recombinosome protein complex. Applicants believe Example 14 is exactly that, an example of the coupling of structural and functional parameters to define a genus, not an absolute rule or law. The Examiner is invited to provide evidence why 95% sequence identity is an acceptable structural parameter, but 90% sequence identity is not, and why enzyme catalysis is an acceptable function, while the functional involvement of a non-enzymatic component

of a complex is not an acceptable functional parameter. The recitation of at least 90% sequence identity is a predictable and easily quantifiable structure of the sequences encompassed by the claims.

Claim 14 has been amended to clarify the level of stringency, "stringent conditions" has been replaced by "high stringency conditions". Support for this amendment is found on page 16, lines 11-13. Claim 14 also follows the format of Example 14. The recitation of a polynucleotide which selectively hybridizes to the full length complement of SEQ ID NO: 1 under explicit high stringency hybridization and wash conditions and which encodes a polypeptide involved in DNA double strand break repair also follows the guideline for claiming a genus of sequences by coupling a structural parameter, *i.e.* hybridization, and a functional parameter, *i.e.* encoding a polypeptide involved in DNA double strand break repair. Further, Applicant has disclosed sequences (SEQ ID NOS: 3, and 5) that would hybridize to the full length complement of SEQ ID NO: 1.

The Examiner is reminded that every species encompassed by the claimed invention need not be disclosed in the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Utter v. Hiraga, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). In fact, the description of a claimed genus can be by structure, formula, chemical name, or physical properties. See Ex parte Maizel, 27 USPQ2d 1662, 1669 (B.P.A.I.1992), (citing Amgen v. Chugai, 927 F.2d 1200, 1206 (Fed. Cir. 1991)). The description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2000). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). A genus of DNAs may be described by means of a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the

scope of the genus, or by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997); see also Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2000). The recitation of a predictable structure of at least 90% sequence identity to SEQ ID NO: 1 is sufficient to satisfy the written description requirement. In addition, an Applicant may rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the claimed invention. Id., citing Lilly at 1568. The Guidelines conclude that one of skill in art would recognize that the Applicants were in possession of the necessary common attributes possessed by the members of the genus.

Applicants have disclosed three isolated polynucleotide sequences and the encoded Rad51C polypeptides in SEQ ID NOS: 1-6, and have provided further guidance on sequence isolation, analysis, and identification, codon degeneracy, conserved protein domains and motifs, as well as conservative amino acid substitutions. The necessary common features of the claimed genus are clear. Applicants clearly had possession of sequences having 90% or 95% sequence identity to SEQ ID NO: 1 or 2, therefore the rejection of claims 2-10, 12, 14-16, 18-26 and 28-35 under 35 U.S.C. §112, first paragraph written description should be withdrawn.

Rejections under 35 U.S.C. §112, 1st Paragraph, New Matter:

Claims 2-10, 12, 14, and 16-34 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not sufficiently described in the specification to indicate the inventor(s) had possession of the invention.

The Examiner asserts that neither the specification nor the original claims provide support for "over the entire length of SEQ ID NO: 1" in claim 12, part (a);

"full-length complement of SEQ ID NO: 1" in claim 14; and "participates in a complex which enhances recombinase activity" in claim 12, part (a).

Applicants respectfully disagree that the terms recited above constituted the introduction of new matter. For example, support for the term "over the entire length of SEQ ID NO: 1" can be found on page 17, line 32 – page 18, line 2, page 20, line 7 – page 21, line 2, especially page 20, lines 8-10. At page 17, line 32 – page 18, line 2, the specification defines the meaning of a "reference" sequence in regards to sequence analyses and comparisons. In the instance case, SEQ ID NO: 1 is clearly the reference sequence to be used for percent sequence identity comparison in claim 12, part (a). At page 20, line 7 – page 21, line 2, the specification describes, as is known in the art, that the GAP algorithm is a global alignment program which finds the optimal alignment of "two complete sequences".

Support for the term "full-length complement of SEQ ID NO: 1" in claim 14 can be found, for example, on page 4, lines 25-28, page 5, lines 6-9, page 12, lines 15-23, and page 14, line 3 – page 15, line 3. For example, on page 5 it states "In another aspect, the present invention relations to an isolated nucleic acid comprising a polynucleotide of a specified length which selectively hybridizes under stringent conditions to a polynucleotide of the present invention, or a complement thereof".

Applicants respectfully disagree that "participates in a complex which enhances recombinase activity" in claim 12, part (a) is not supported in the specification or claims as filed. However, in order to expedite prosecution, claim 12, part (a) (and claims14, and 25) have been amended to recite that the encoded polypeptide is "involved in DNA double strand break repair". Support for this amendment is found on pages 1-4, which describe the function of the Rad51 family, specifically support is found on page 2, line 22 – page 3, line 2, and page 4, lines 7-11. This amendment obviates the rejection of claim 12, part (a).

Applicants have properly pointed to support and addressed by argument and amendment the rejection of claims 2-10, 12, 14, and 16-34 under 35 U.S.C. §112,

first paragraph, as containing new matter, and therefore respectfully request that the rejection be withdrawn and not applied to the amended claims.

Rejections under 35 U.S.C. §112, 2nd Paragraph:

Claims 2-10, 12, and 14-35 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is repeated for the reasons of record set forth in the Office Actions mailed 11/8/01, and 7/1/02. The Examiner continues to assert that the term "selectively hybridizes" is unclear, and that the conditions for hybridization must include the time of the wash.

Applicants respectfully disagree for the reasons of record. Further, Applicants have amended claim 14 to further clarify the claim, "stringent conditions" has been replaced with "high stringency conditions", as is recited on page 16, lines 11-13 of the specification. Applicants submit the excerpt of Ausubel *et al.* referred to in the previous response in Appendix F of the current amendment. The term "selectively hybridizes" is clear to one of skill in the art, as are the bounds of the hybridization conditions even if the time of the wash is not explicitly recited. MPEP 2173.02 further clarifies the issue of clarity and precision,

> "The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C 112 second paragraph is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. ... Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) the content of the particular application disclosure;
> (B) the teachings of the prior art; and
> (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

Applicants submit that claim 14 meets the above criteria for clarity as selectively hybridizes is explicitly defined in the specification as pointed to in previous responses, and the claim further includes specific high stringency hybridization and wash conditions as defined in the specification, none of these terms is defined in such a way to be contrary to their ordinary meaning in the art. Further, it is illogical to interpret the claim listing specific high stringency hybridization and wash conditions to include ridiculously non-stringent time parameters for the wash, *e.g.* 1 minute, as suggested by the Examiner.

Therefore it is respectfully requested that the rejection of claims 2-10, 12, and 14-35 under 35 U.S.C. §112, second paragraph, as being indefinite be withdrawn.

Claims 12, 14, and 25 are also rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner asserts that it is "unclear what it means for a protein to participate in a complex", and "unclear what it means to enhance recombinase activity".

Applicant respectfully disagrees that the phrase "polypeptide which participates in a complex which enhances recombinase activity" in unclear to one of skill in the art. However, in order to expedite prosecution, claims 12, 14, and 25 have been amended to recite a "polypeptide involved in DNA double strand break repair". Support for this amendment is found on pages 1-4, which describe the function of the Rad51 family, specifically support is found on page 2, line 22 – page 3, line 2, and page 4, lines 7-11. Given the support in the specification and the knowledge of one of skill in the pertinent art, the claim recites a clear and specific function for the encoded polypeptides. Therefore it is respectfully requested that the rejection of claims 12, 14, and 25 under 35 U.S.C. §112, second paragraph, as being indefinite be withdrawn.

Rejections under 35 U.S.C. §102:

Claim 14 is rejected under 35 U.S.C. §102(a) as being anticipated by NCI-CGAP (GenBank Accession No. AI184177). The rejection is repeated for the

reasons of record. The Examiner asserts that the sequence AI184177 would hybridize to the full-length complement of SEQ ID NO: 1 under the conditions recited in claim 14.

Applicants respectfully disagree for the reasons of record. The sequence disclosed in AI184177 would not selectively hybridize to the full length complement of SEQ ID NO: 1 under the explicit high stringency conditions recited in claim 14. Applicant submits in Appendix G two global alignments of AI184177 with SEQ ID NO: 1 as determined by the GAP algorithm under default parameters. The first GAP alignment for the forward orientation of AI184177 shows 40.751% sequence identity to SEQ ID NO: 1 with the longest region(s) of identity being 6 contiguous nucleotides. The second GAP alignment in Appendix G aligns the reverse orientation of AI184177 with SEQ ID NO: 1, and shows 44.139% sequence identity with the longest region of identity being 11 contiguous nucleotides. Clearly, the polynucleotide of AI184177 would not be expected to selectively hybridize to SEQ ID NO: 1 even under low stringency conditions, much less under the high stringency conditions explicitly recited in the claim. Therefore Applicants respectfully request that the rejection of claim 14 under 35 USC §102(a) as being anticipated by NCI-CGAP (GenBank Accession No. AI184177) be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments, it is believed that claims 2-10, 12, 14 and 16-34 are in condition for allowance. Withdrawal of the outstanding rejections and allowance of all of the remaining claims is respectfully requested. The Examiner is invited to telephone the Applicant if this would expedite the prosecution and allowance of the instant application.

Respectfully submitted,

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